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(54) **NOVEL QUINUCLIDINE DERIVATIVES AND THEIR PHARMACEUTICAL USE**

NEUE CHINUKLIDINDERIVATIVE UND DEREN PHARMAZEUTISCHE VERWENDUNG

NOUVEAUX DERIVES DE QUINUCLIDINE ET LEUR UTILISATION PHARMACEUTIQUE

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Description

TECHNICAL FIELD

[0001] This invention relates to novel quinuclidine derivatives and their use as pharmaceuticals. Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

BACKGROUND ART

[0002] The endogenous cholinergic neurotransmitter, acetylcholine, exerts its biological effect via two types of cholinergic receptors, the muscarinic Acetyl Choline Receptors (mAChR) and the nicotinic Acetyl Choline Receptors (nAChR).

[0003] It is well established that muscarinic acetylcholine receptors are of importance in relation to memory and cognition, and much research aimed at the development of agents for the treatment of memory related disorders have focused on the synthesis of muscarinic acetylcholine receptor modulators.

[0004] Indeed several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency or a serotonergic deficiency.

[0005] Brown *et al.* [Brown *et al.*: Quinuclidine Inhibitors of 2,3-Oxidosqualene Cyclase-Lanosterol Synthase: Optimization from Lipid Profiles; J. Med. Chem. 1999 42 1306-1311] describe the synthesis of 3-substituted quinuclidine derivatives useful as inhibitors of the cholesterol biosynthesis. An effect on the nicotinic and/or the monoamine receptors is not reported.

[0006] WO 02/44176 describes 3-substituted quinuclidine derivatives and their use as nicotinic agonists.

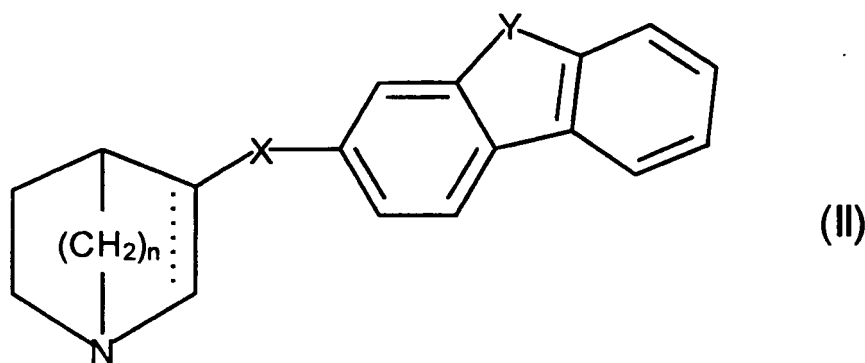
SUMMARY OF THE INVENTION

[0007] The present invention is devoted to the provision of new quinuclidine derivatives that are modulators of the nicotinic and/or of the monoamine receptors, and which modulators are useful for the treatment of diseases or disorders related to the cholinergic receptors, and in particular the nicotinic acetylcholine receptor, the monoamine receptors, in particular the serotonin receptor (5-HT₁), the dopamine receptor (DAR) and the norepinephrine receptor (NER), and of the biogenic amine transporters for serotonin (5-HT), dopamine (DA) and norepinephrine (NE).

[0008] Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

[0009] The compounds of the invention may also be useful as diagnostic tools or monitoring agents in various diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging), and they may be used in labelled or unlabelled form.

[0010] Accordingly, in its first aspect the invention provides quinuclidine derivatives represented by Formula II

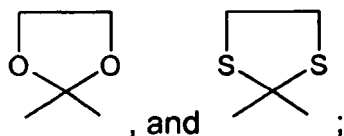


wherein,

----- represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -C(=CH₂)-, -NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



and

Y represents O, S, SO₂, or NR', wherein R' represents hydrogen or alkyl.

[0011] In another aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the quinuclidine derivative of the invention.

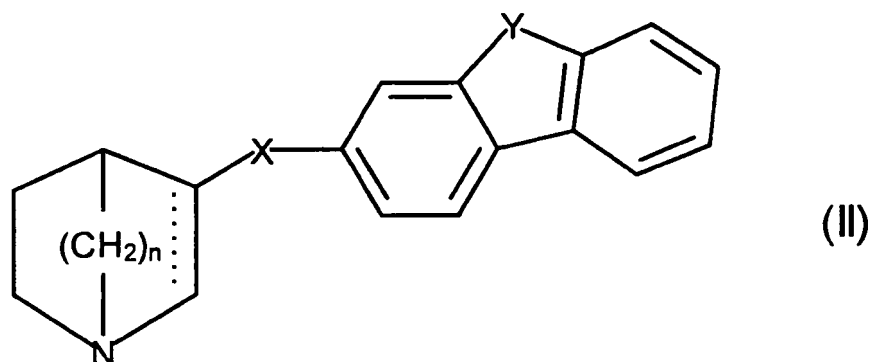
[0012] In a third aspect the invention relates to the use of the quinuclidine derivative of the invention, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the action of a nicotinic acetylcholine receptor modulator.

[0013] Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Quinuclidine Derivatives

[0014] In a preferred embodiment the quinuclidine derivative of the invention is a compound of Formula II

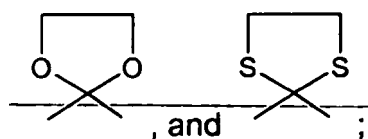


wherein

----- represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -C(=CH₂)-, -NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



and

Y represents O, S, SO₂, or NR', wherein R' represents hydrogen or alkyl.

[0015] In a more preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula II, wherein ----- represents a single (covalent) bond.

[0016] In another preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula II, wherein n is 1, 2 or 3.

[0017] In a third preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula II, wherein X represents a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, and -CH₂-.

[0018] In a fourth preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula II, wherein Y represents O, S, SO₂, or NR', wherein R' represents hydrogen or alkyl.

[0019] In a most preferred embodiment the quinuclidine derivative of the invention of Formula II is

(±)-3-(Dibenzofuran-2-yloxy)-1-azabicyclo[2.2.2]octane;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

[0020] Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

Definition of Substituents

[0021] In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C₁₋₁₈-alkyl), more preferred of from one to six carbon atoms (C₁₋₆-alkyl); lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C₁₋₄-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C₁₋₃-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

Pharmaceutically Acceptable Salts

[0022] The quinuclidine derivative of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the quinuclidine derivative of the invention.

[0023] Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzenesulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphononic acid, the naphthalene-2-sulphonate derived from naphthalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphononic acid, and the like. Such salts may be formed by procedures well known and described in the art.

[0024] Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

[0025] Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysine, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

[0026] In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts (aza-onium salts). Preferred aza-onium salts include the alkyl-onium salts, in particular the methyl- and the ethyl-onium salts; the cycloalkyl-onium salts, in particular the cyclopropyl-onium salts; and the cycloalkylalkyl-onium salts, in particular the cyclopropyl-methyl-onium salts.

Steric Isomers

[0027] The quinuclidine derivatives of the present invention may exist in (+) and (-) forms as well as in racemic forms (±). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

[0028] Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

[0029] The quinuclidine derivatives of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

[0030] Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by Jacques J, Collet A, & Wilen S in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

[0031] Optical active compounds can also be prepared from optical active starting materials.

Methods of Preparation

[0032] The quinuclidine derivatives of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

[0033] Also one compound of the invention can be converted to another compound of the invention using conventional methods.

[0034] The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

[0035] The present invention relates to novel quinuclidine derivatives, which are found to be cholinergic ligands at the nicotinic acetylcholine receptors (nAChR), and modulators of the monoamine receptors, in particular the biogenic amine transporters such as the serotonin receptor (5-HT₁), the dopamine receptor (DAR) and the norepinephrine receptor (NER), and of the biogenic amine transporters for serotonin (5-HT), dopamine (DA) and norepinephrine (NE). Also preferred quinuclidine derivatives of the invention show selective α_7 activity, as shown in the working examples. The compounds of the present invention may in particular be agonists, partial agonists, antagonists and allosteric modulators of the receptor.

[0036] Due to their pharmacological profile the quinuclidine derivatives of the invention may be useful for the treatment of diseases or conditions as diverse as CNS related diseases, PNS related diseases, diseases related to smooth muscle contraction, endocrine disorders, diseases related to neuro-degeneration, diseases related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

[0037] In a preferred embodiment the quinuclidine derivatives of the invention are used for the treatment of diseases, disorders, or conditions relating to the central nervous system. Such diseases or disorders includes anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, psychosis, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

[0038] In a preferred embodiment diseases, disorders, or conditions relating to the central nervous system for which the quinuclidine derivatives of the invention are used are cognitive disorders, psychosis, schizophrenia and/or depression.

[0039] In another preferred embodiment the quinuclidine derivatives of the invention may be useful for the treatment of diseases, disorders, or conditions associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

[0040] In yet another preferred embodiment the quinuclidine derivatives of the invention may be useful for the treatment of endocrine disorders, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

[0041] In still another preferred embodiment the quinuclidine derivatives of the invention may be useful for the treatment of neurodegenerative disorders, including transient anoxia and induced neurodegeneration.

[0042] In even another preferred embodiment the quinuclidine derivatives of the invention may be useful for the

treatment of inflammatory diseases, disorders, or conditions, including inflammatory skin disorders such as acne and rosacea, Crohn's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

[0043] In still another preferred embodiment the quinuclidine derivatives of the invention may be useful for the treatment of mild, moderate or even severe pain of acute, chronic or recurrent character, as well as pain caused by migraine, postoperative pain, and phantom limb pain. The pain may in particular be neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.

[0044] Finally the quinuclidine derivatives of the invention may be useful for the treatment of withdrawal symptoms caused by termination of use of addictive substances. Such addictive substances include nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol. Withdrawal from addictive substances is in general a traumatic experience characterised by anxiety and frustration, anger, anxiety, difficulties in concentrating, restlessness, decreased heart rate and increased appetite and weight gain.

[0045] In this context "treatment" covers treatment, prevention, prophylactics and alleviation of withdrawal symptoms and abstinence as well as treatment resulting in a voluntary diminished intake of the addictive substance.

[0046] In another aspect, the quinuclidine derivatives of the invention are used as diagnostic agents, e.g. for the identification and localisation of nicotinic receptors in various tissues.

Pharmaceutical Compositions

[0047] In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the quinuclidine derivatives of the invention.

[0048] While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

[0049] In a preferred embodiment, the invention provides pharmaceutical compositions comprising the quinuclidine derivative together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

[0050] The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by a person skilled in the art by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

[0051] Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

[0052] The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

[0053] The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

EXAMPLES

[0054] The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

[0055] General remarks: All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulfate was used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

Method G

(±)-3-(Dibenzofuran-2-yloxy)-1-azabicyclo[2.2.2]octane fumaric acid salt(Compound G1)

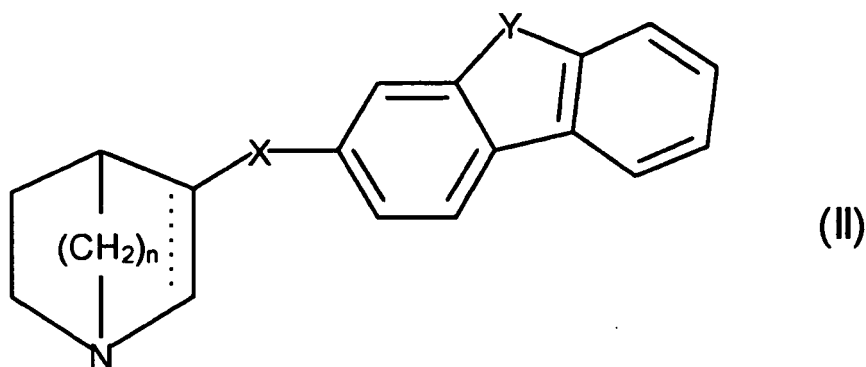
[0056] To a mixture of (±)-3-quinuclidinol (3.0 g, 23.6 mmol), 2-hydroxydibenzofuran (4.3 g, 23.6 mmol), triphenylphosphine (9.29 g, 35.4 mmol) and THF, was added: diethylazodicarboxylate (6.3 ml, 35.4 mmol) over a time period of 40 min at room temperature. The mixture was stirred at 50°C for 7 days. Aqueous sodium hydroxide (100 ml, 1 M) was added. The mixture was extracted with dichloromethane (3 x 100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 2.0 g (29%).

[0057] The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 131.3-133.8°C.

[0058] The compound also may be named (±)-3-(Dibenzofuran-2-yloxy)-quinuclidine.

Claims

1. A quinuclidine derivative represented by Formula II

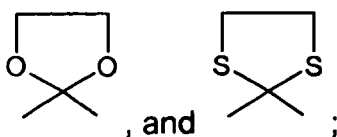


wherein

----- represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -S-, -SO-, -SO₂-, -CH₂-, -C(=CH₂)-, -NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



and

Y represents O, S, SO₂, or NR', wherein R' represents hydrogen or alkyl.

2. The quinuclidine derivative of claim 1, wherein ----- represents a single (covalent) bond.

3. The quinuclidine derivative of either one of claims 1-2, wherein n is 1, 2 or 3.

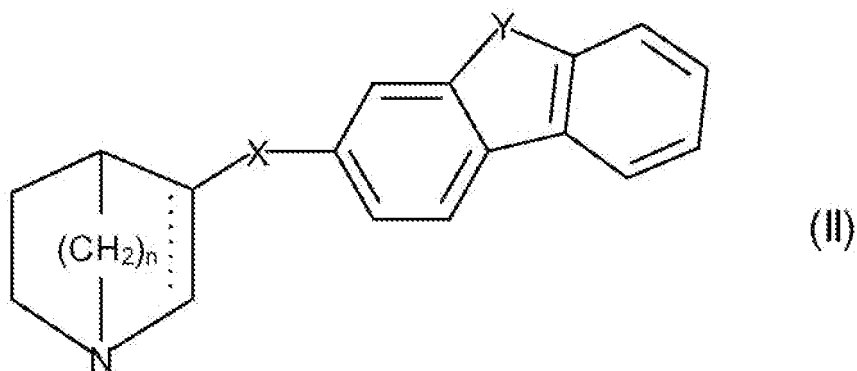
4. The quinuclidine derivative of any one of claims 1-3, wherein X represents a linker selected from -O-, -S-, and -CH₂-.

5. The quinuclidine derivative of any one of claims 1-4, wherein Y represents O, S, SO₂, or NR', wherein R' represents hydrogen or alkyl.

6. The quinuclidine derivative of claim 5, which is
(±)-3-(Dibenzofuran-2-yloxy)-1-azabicyclo[2.2.2]octane;
or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof.
7. A pharmaceutical composition comprising a therapeutically effective amount of a quinuclidine derivative of any one
of claims 1-6, or a pharmaceutically-acceptable addition salt thereof.
8. Use of a quinuclidine derivative of any one of claims 1-6, or a pharmaceutically-acceptable addition salt thereof, for
the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease
or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to
modulation of cholinergic receptors and/or monoamine receptors.
9. The use according to claim 8, wherein the disease, disorder or condition relates to the central nervous system.
10. The use according to claim 9, wherein the disease, disorder or condition is anxiety, cognitive disorders, learning
deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit hyperactivity disorder
(ADHD), Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome,
psychosis, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic
disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia,
senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-
traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syn-
drome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.
11. The use according to claim 8, wherein the disease, disorder or condition are associated with smooth muscle con-
tractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epi-
lepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.
12. The use according to claim 8, wherein the disease, disorder or condition is related to the endocrine system, such
as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.
13. The use according to claim 8, wherein the disease, disorder or condition is a neurodegenerative disorders, including
transient anoxia and induced neuro-degeneration.
14. The use according to claim 8, wherein the disease, disorder or condition is an inflammatory disorder, including
inflammatory skin disorders such as acne and rosacea, Crohn's disease, inflammatory bowel disease, ulcerative
colitis, and diarrhoea.
15. The use according to claim 8, wherein the disease, disorder or condition is mild, moderate or even severe pain of
acute, chronic or recurrent character, pain caused by migraine, postoperative pain, phantom limb pain, neuropathic
pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to pe-
ripheral nerve injury.
16. The use according to claim 8, wherein the disease, disorder or condition is associated with withdrawal symptoms
caused by termination of use of addictive substances, including nicotine containing products such as tobacco, opioids
such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.

Patentansprüche

1. Chinuclidinderivat, das durch Formel II wiedergegeben ist

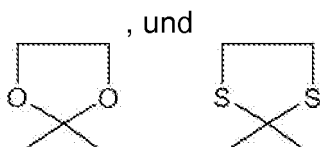


15 wobei

----- eine optionale Doppelbindung bedeutet;

n 1, 2 oder 3 ist;

20 X eine Verbindungseinheit ausgewählt aus -O-, -S-, -SO-, -SO₂-, -CH₂-, -C(=CH₂)-, -NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



30 bedeutet; und

Y O, S, SO₂ oder NR' bedeutet, wobei R' Wasserstoff oder Alkyl bedeutet.

2. Chinuclidinderivat nach Anspruch 1, wobei ----- eine (kovalente) Einfachbindung bedeutet.

35 3. Chinuclidinderivat nach einem der Ansprüche 1-2, wobei n 1, 2 oder 3 ist.

4. Chinuclidinderivat nach einem der Ansprüche 1-3, wobei X eine Verbindungseinheit ausgewählt aus -O-, -S- und -CH₂- bedeutet.

40 5. Chinuclidinderivat nach einem der Ansprüche 1-4, wobei Y O, S, SO₂ oder NR' bedeutet, wobei R' Wasserstoff oder Alkyl bedeutet.

6. Chinuclidinderivat nach Anspruch 5, welches (±)-3-(Dibenzofuran-2-yloxy)-1-azabicyclo[2.2.2]octan ist; oder ein Enantiomer davon, oder ein pharmazeutisch verträgliches Additionssalz davon, oder ein Oniumsalz davon.

45 7. Pharmazeutische Zusammensetzung umfassend eine therapeutisch wirksame Menge von einem Chinuclidinderivat nach einem der Ansprüche 1-6, oder einem pharmazeutisch verträglichen Additionssalz davon.

8. Verwendung von einem Chinuclidinderivat nach einem der Ansprüche 1-6, oder einem pharmazeutisch verträglichen Additionssalz davon, für die Herstellung einer pharmazeutischen Zusammensetzung/eines Medikaments für die Behandlung, Verhütung oder Linderung einer Krankheit oder einer Störung oder eines Zustands eines Säugers, einschließlich eines Menschen, wobei die Krankheit, die Störung oder der Zustand auf die Modulation von cholinergen Rezeptoren und/oder Monoaminrezeptoren anspricht.

50 9. Verwendung nach Anspruch 8, wobei sich die Krankheit, die Störung oder der Zustand auf das Zentralnervensystem bezieht.

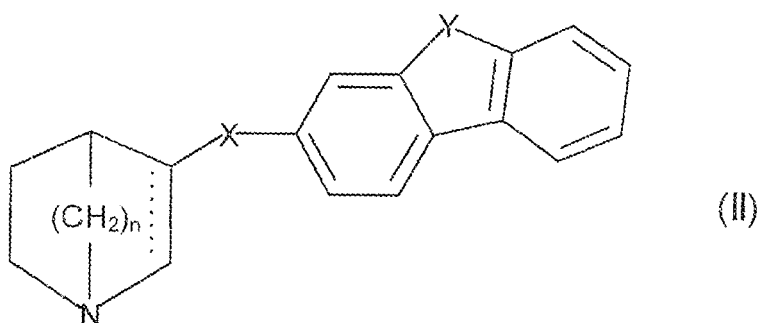
10. Verwendung nach Anspruch 9, wobei es sich bei der Krankheit, der Störung oder dem Zustand um Angst, kognitive

Störungen, ein Lerndefizit, Gedächtnisdefizite und eine Gedächtnisdysfunktion, die Alzheimer-Krankheit, ein Aufmerksamkeitsdefizit, eine Aufmerksamkeitsdefizit-Hyperaktivitätsstörung (ADHD), die Parkinson-Krankheit, Chorea Huntington, amyotrophe Lateralsklerose, das Gilles de la Tourette-Syndrom, eine Psychose, eine Depression, eine Manie, eine manische Depression, Schizophrenie, Zwangsstörungen (OCD), Panikstörungen, Essstörungen wie Anorexia nervosa, Bulimie und Fettleibigkeit, Narkolepsie, Nozizeption, AIDS-Demenz, senile Demenz, periphere Neuropathie, Autismus, Dyslexie, tardive Dyskinesie, Hyperkinesie, Epilepsie, Bulimie, das posttraumatische Syndrom, eine Sozialphobie, Schlafstörungen, Pseudodemenz, das Ganser-Syndrom, das prämenstruelle Syndrom, das Syndrom der späten Lutealphase, das chronische Ermüdungssyndrom, Mutismus, Trichotillomanie und Jet-lag handelt.

11. Verwendung nach Anspruch 8, wobei die Krankheit, die Störung oder der Zustand mit Kontraktionen eines glatten Muskels zusammenhängen, einschließlich konvulsiver Störungen, Angina pectoris, einer Frühgeburt, Krämpfen, Diarrhö, Asthma, Epilepsie, tardiver Dyskinesie, Hyperkinesie, vorzeitiger Ejakulation und Erektionsschwierigkeiten.
12. Verwendung nach Anspruch 8, wobei sich die Krankheit, die Störung oder der Zustand auf das endokrine System bezieht, wie etwa Thyreotoxikose, Phäochromozytom, Hochdruck und Arrhythmien.
13. Verwendung nach Anspruch 8, wobei es sich bei der Krankheit, der Störung oder dem Zustand um eine neurodegenerative Störung handelt, einschließlich vorübergehender Anoxie und induzierter Neurodegeneration.
14. Verwendung nach Anspruch 8, wobei es sich bei der Krankheit, der Störung oder dem Zustand um eine entzündliche Störung, einschließlich entzündlicher Hautstörungen wie Akne und Rosacea, Morbus Crohn, entzündlicher Darm-erkrankung, Colitis ulcerosa und Diarrhö, handelt.
15. Verwendung nach Anspruch 8, wobei es sich bei der Krankheit, der Störung oder dem Zustand um milde, mäßige oder auch starke Schmerzen von akutem, chronischem oder wiederkehrendem Charakter, durch Migräne verursachte Schmerzen, postoperative Schmerzen, Phantomschmerzen, neuropathische Schmerzen, chronische Kopfschmerzen, zentrale Schmerzen, Schmerzen in Verbindung mit diabetischer Neuropathie, mit posttherapeutischer Neuralgie oder mit einer peripheren Nervenverletzung handelt.
16. Verwendung nach Anspruch 8, wobei die Krankheit, die Störung oder der Zustand mit Entzugssymptomen zusammenhängt, die durch die Beendigung des Gebrauchs von süchtigmachenden Substanzen, einschließlich nikotin- haltiger Produkte wie Tabak, Opioide wie Heroin, Kokain und Morphin, Benzodiazepine und benzodiazepinartiger Drogen bzw. Arzneimittel, und Alkohol, verursacht sind.

Revendications

1. Dérivé de quinuclidine représenté par la formule II

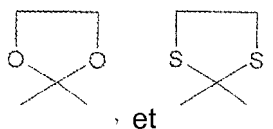


dans laquelle

----- représente une liaison double facultative ;

n est 1, 2 ou 3 ;

X représente un lieu choisi parmi -O-, -S-, -SO-, -SO₂-, -CH₂-, -C(=CH₂)-, -NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



et

Y représente O, S, SO₂ ou NR', où R' représente un hydrogène ou un alkyle.

- 10 **2.** Dérivé de quinuclidine selon la revendication 1, dans lequel X représente une liaison simple (covalente).
- 3.** Dérivé de quinuclidine selon l'une quelconque des revendications 1-2, dans lequel n est 1, 2 ou 3.
- 15 **4.** Dérivé de quinuclidine selon l'une quelconque des revendications 1 à 3, dans lequel X représente un lieu choisi parmi -O-, -S- et -CH₂-.
- 5.** Dérivé de quinuclidine selon l'une quelconque des revendications 1 à 4, dans lequel Y représente O, S, SO₂ ou NR', où R' représente un hydrogène ou un alkyle.
- 20 **6.** Dérivé de quinuclidine selon la revendication 5, qui est le (±)-3-(dibenzofuran-2-yloxy)-1-azabicyclo[2.2.2]octane ; ou un énantiomère de celui-ci, ou un sel d'addition pharmaceutiquement acceptable de celui-ci ou un sel d'onium de celui-ci.
- 25 **7.** Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un dérivé de quinuclidine selon l'une quelconque des revendications 1 à 6, ou d'un sel d'addition pharmaceutiquement acceptable de celui-ci.
- 8.** Utilisation d'un dérivé de quinuclidine selon l'une quelconque des revendications 1 à 6, ou d'un sel d'addition pharmaceutiquement acceptable de celui-ci, pour la fabrication d'une composition pharmaceutique/médicament pour le traitement, la prévention ou l'atténuation d'une maladie ou d'un trouble ou d'un état d'un mammifère, incluant

30 un être humain, laquelle maladie, lequel trouble ou état réagit à une modulation des récepteurs cholinergiques et/ou des récepteurs monoamines.
- 9.** Utilisation selon la revendication 8, dans laquelle la maladie, le trouble ou l'état est lié(e) au système nerveux central.
- 35 **10.** Utilisation selon la revendication 9, dans laquelle la maladie, le trouble ou l'état est une anxiété, des troubles cognitifs, une déficience d'apprentissage, des déficiences et un dysfonctionnement de la mémoire, une maladie d'Alzheimer, une déficience de l'attention, un trouble d'hyperactivité avec déficience de l'attention (THADA), une maladie de Parkinson, une maladie de Huntington, une sclérose latérale amyotrophique, un syndrome de Gilles de la Tourette, une psychose, une dépression, une manie, une manie-dépression, une schizophrénie, des troubles obsessionnels-compulsifs (TOC), des troubles paniques, des troubles de l'alimentation tels qu'une anorexie mentale, une boulimie

40 et une obésité, une narcolepsie, une nociception, une démence liée au SIDA, une démence sénile, une neuropathie périphérique, un autisme, une dyslexie, une dyskinésie tardive, une hyperkinésie, une épilepsie, une boulimie, un syndrome post-traumatique, une phobie sociale, des troubles du sommeil, une pseudodémence, un syndrome de Ganser, un syndrome prémenstruel, un syndrome de phase lutéale tardive, un syndrome de fatigue chronique, un mutisme, une trichotillomanie et un décalage horaire.
- 45 **11.** Utilisation selon la revendication 8, dans laquelle la maladie, le trouble ou l'état sont associés à des contractions des muscles lisses, incluant des troubles convulsifs, une angine de poitrine, un travail prématuré, des convulsions, une diarrhée, un asthme, une épilepsie, une dyskinésie tardive, une hyperkinésie, une éjaculation prématurée et une difficulté d'érection.
- 50 **12.** Utilisation selon la revendication 8, dans laquelle la maladie, le trouble ou l'état est lié(e) au système endocrinien, comme une thyrotoxicose, un phéochromocytome, une hypertension et des arythmies.
- 55 **13.** Utilisation selon la revendication 8, dans laquelle la maladie, le trouble ou l'état est un trouble neurodégénératif, incluant une anoxie transitoire et une neurodégénérescence induite.
- 14.** Utilisation selon la revendication 8, dans laquelle la maladie, le trouble ou l'état est un trouble inflammatoire, incluant

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des troubles cutanés inflammatoires tels qu'une acné et une rosacée, une maladie de Crohn, une maladie intestinale inflammatoire, une rectocolite hémorragique et une diarrhée.

5 **15.** Utilisation selon la revendication 8, dans laquelle la maladie, le trouble ou l'état est une douleur légère, modérée ou même sévère de caractère aigu, chronique ou récurrent, une douleur provoquée par une migraine, une douleur postopératoire, une douleur de membre fantôme, une douleur neuropathique, une céphalée chronique, une douleur centrale, une douleur liée à une neuropathie diabétique, à une névralgie thérapeutique ou à une lésion d'un nerf périphérique.

10 **16.** Utilisation selon la revendication 8, dans laquelle la maladie, le trouble ou l'état est associé(e) à des symptômes de manque provoqués par l'arrêt d'utilisation de substances toxicomanogènes, incluant les produits contenant de la nicotine tels que le tabac, les opioïdes tels que l'héroïne, la cocaïne et la morphine, les benzodiazépines et les substances médicamenteuses de type benzodiazépine, et l'alcool.

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REFERENCES CITED IN THE DESCRIPTION

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